REMARKS

Claims 1, 3-8, 36 and 37 are pending.

Claim 2 has been cancelled without prejudice.

Claims 1, 3, 4, and 6 have been amended. A document entitled "Version With Markings to Show Changes Made" setting forth a marked-up version of the amended specification and claims is attached hereto.

I. Amendments to the specification.

The specification was objected to for recitation of SEQ ID NO:9 in reference to *polypeptides* when this sequence is, in fact, a polynucleotide sequence. The paragraphs beginning on page 23, line 3, and beginning on page 24, line 25 , have been amended to correct this inadvertent error. In addition, the paragraph beginning on page 4, line 4 has been amended to correct certain obvious typographical errors.

II. Amended Claims 1, 3, 4, and 6.

Claim 1 has been amended to incorporate the molecular size limitation of cancelled claim 2 (e.g., at least about 46 kilodaltons) and to add a clarifying statement that the basis of the molecular size is relative to full length tryptophanyl-tRNA synthetase having a size of about 54 kilodaltons. Support for this amendment can be found in original claim 2 and in the specification at page 59, line 29 where the molecular weight of full length tryptophanyl-tRNA synthetase is disclosed.

Claims 3 and 6 have been amended to recite *tryptophanyl-tRNA* synthetase for consistency with claim 1, from which they depend.

Claim 4 has been amended to correct an inadvertent error in referring to tryptophanyl-tRNA synthetase as angiogenic. Amended claim 4 is now directed to a polypeptide of claim 1 which is angiostatic. Support for this amendment can be found in Example 6 on page 56 and in Example 7 on page 57.

III. Claims 1, 3, 6, and 36 are not indefinite.

Claims 3 and 6 have been rejected for failure to comply with the requirements of the second paragraph of 35 U.S.C. §112 as being indefinite for reciting "truncated tRNA" synthetase rather than "truncated *tryptophanyl*-tRNA" synthetase as used in parent claim 1. Applicants do not believe that the recited term renders the claims

indefinite; however, claims 3 and 6 have been amended in accordance with the Examiner's suggestion to expedite prosecution of the application. This ground of rejection is now moot.

The Office Action also states that claims 1, 6, and 36 are "vague and indefinite for reciting 'and fragments thereof comprising the amino acid sequence -Asp-Leu-Thr-' in Claim 6 as it is not clear how this limitation further defines the independent claim." (Paper No. 9, page 4, lines 3-5). Applicants do not understand this rejection. Claim 1 does not recite this limitation, nor does claim 36, which depends directly from claim 1. Therefore, neither claim 1 nor claim 36 is vague or indefinite on this basis. Claims 6 and *37, which depends from claim 6* do recite this limitation. This claim limitation simply means that polypeptides corresponding to portions (i.e., fragments) of the other members of the Markush group are also specifically claimed, so long as they include a DLT tripeptide sequence and meet the additional requirements of having a size of at least about 46 kilodaltons and being capable of regulating vascular endothelial cell function as required by parent claim 1. The recited limitation is clear on its face. Applicants respectfully request reconsideration and withdrawal of this ground for rejection.

In summary, all of the present claims meet the requirements of 35 U.S.C. §112, second paragraph. The rejections of claims 1, 4, 6 and 36 should be withdrawn.

IV. Claims 1, 4, 6, and 37 meet all requirements of 35 U.S.C. §112, first paragraph.

Claims 1 and 4 have been rejected as failing to meet the requirements of the first paragraph of 35 U.S.C. §112, as containing subject matter which was not described in the specification in a way that showed that the inventors had possession of the claimed invention at the time the application was filed. It is not clear from the Office Action what is the specific objection with regard to claim 1. Applicants note that claim 2 was not rejected. Amended claim 1 is equivalent in scope to cancelled claim 2. As such, this ground of rejection for claim 1 should be withdrawn.

Regarding claim 4, the Office Action takes issue with the limitation that the tryptophanyl-tRNA synthetase be "angiogenic" since the specification indicated that these materials are *angiostatic*. Claim 4 is now directed to polypeptides of claim 1 that are angiostatic. Therefore, this ground of rejection is no longer applicable.

Claims 1, 6 and 37 have also been rejected under the first paragraph of 35 U.S.C. §112, because the specification purportedly is not enabling for the subject matter claimed. Again, Applicants point out that claim 2 was not rejected on this ground, and present claim 1 is equivalent in scope to cancelled claim 2. Therefore, this rejection should be withdrawn with respect to claim 1.

Regarding claims 6 and 37, the Office Action states that the specification is not enabling for the limitation "and fragments thereof comprising the amino acid sequence -Asp-Leu-Thr-". Applicants respectfully submit that one of ordinary skill in the art at the time the application was filed would have been able to practice the full scope claimed invention based on the description in the specification. In particular, the specification describes methods for cleaving polypeptides, and specifically includes examples of such cleavage in Example 4, page 53 and Example 11 on page 59. To obtain a "fragment" of one of the other members of the Markush group, one merely exposes the specified truncated tryptophanyl-tRNA synthetase to protease enzymes. The determination of protein molecular weight is old in the art and is described in the specification, for example in Example 11, on page 59. The presence of a contiguous DLT sequence in any isolated fragment can be determined by sequencing the fragment. Furthermore, the specification is replete with detailed descriptions for assaying vascular endothelial cell function activity of such fragments. Thus, methods for determining all of the characteristics necessary to identify fragments within the scope of the claims are described n the specification, and many are well known in the art.

In addition, as noted above, claim 2 was not rejected on this basis and claims 6 and 37 now incorporate all of the limitations of original claim 2 by virtue of the amendment to claim 1. It is hard to imagine a situation where the full scope of a parent claim is enabled, but the scope of a narrower, dependent claim is not. Applicants respectfully request that this rejection be withdrawn.

V. Claims 1, 4-8, 36 and 37 are Patentable over Fleckner *et al.*

Claims 1, 3-8, 36 and 37 have been rejected under 35 U.S.C. §102(b) as being anticipated by Fleckner *et al.* (*Proc. Natl. Acad. Sci.*, Vol. 88, pp. 11520-11524 (1991)). Applicant does not understand this rejection since Fleckner *et al.* disclose only full length tryptophanyl-tRNA synthetase, which has a molecular weight of about 54 kilodaltons

(see page 11521, first column, first paragraph under the heading RESULTS). All of the present claims are directed to truncated tryptophanyl-tRNA synthetase polypeptides having a size of at least about 46 kilodaltons Truncated polypetides are, by definition, not full length. The assertion that this reference discloses truncated tryptophanyl synthetase is unfounded. Fleckner *et al.* do not anticipate the present claims and this rejection should be withdrawn.

VI. Claims 1, 3-5, 7, 8, 36 and 37 are Patentable over Lemarie *et al.*

Claims 1, 3-5, 7, 8, 36 and 37 have been rejected under 35 U.S.C. §102(b) as being anticipated by Lemarie *et al.* (*Eur. J. Biochem.*, Vol. 51, pp. 237-252 (1975)). Lemarie *et al.* disclose the isolation of full length tryptophanyl-t-RNA synthetase and two lower molecular weight variants thereof. According to Lemarie *et al.*, full length tryptophanyl-tRNA synthetase is a dimeric protein having a molecular size of about 108 kilodaltons, and consisting of two identical chains of 54 kilodalton size (see Lemarie et al., page 242, first col., first paragraph, and Table 1). This description is in agreement with the description of tryptophanyl-tRNA synthetase in the present application. Lemarie *et al.* also describe shortened versions of the enzyme having molecular sizes of 85 kilodaltons and 82 kilodaltons, each of which are also dimers consisting of two identical polypeptides having a molecular size of about 41 kilodaltons (*Id.*). Lemarie *et a*l. do not teach or suggest a truncated tryptophanyl-tRNA synthetase having a size of at least about 46 kilodaltons based on a full length tryptophanyl-tRNA synthetase having a size of about 54 kilodaltons as required by all of the present claims. Furthermore, Lemarie *et al.* do not teach or suggest a truncated tryptophanyl-tRNA synthetase having a Rossman fold domain that can regulate vascular endothelial cell function, as required by all of the present claims. Therefore, all of the present claims are patentable over Lemarie *et al.*

VII. Conclusion.

Claims 1, 3-8, 36 and 37 are in full compliance with the requirements of 35 U.S.C. §112 and are patentable over the applied art. Early allowance of all claims is solicited.

Respectfully submitted,

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Version With Markings To Show Changes Made

In the specification:

The paragraph beginning on page 4, line 4 has been amended to read:

The truncated ~~tryptophanol~~tryptophanyl tRNA synthetase derived polypeptides have an amino-terminal truncation but may include a Rossmann fold nucleotide binding domain. The isolated polypeptide is capable of regulating vascular endothelial cell function and preferably has a size of at least ~~bout~~about 46 kiloDaltons (kD).

The paragraph beginning on page 23, line 3 has been amended to read:

The present invention further relates to variants of the hereinabove described polynucleotides which encode for fragments, analogs and derivatives of the ~~polypeptide having the amino acid~~polynucleotide having the nucleic acid sequence of SEQ ID NO:9 or the polypeptide encoded by the cDNA of SEQ ID NO:9. The variant of the polynucleotide may be a naturally occurring allelic variant of the polynucleotide or a non-naturally occurring variant of the polynucleotide. Thus, the present invention includes polynucleotides encoding the same mature polypeptide as shown in SEQ ID NO:~~9~~10 or the same mature polypeptide encoded by the cDNA of SEQ ID NO:9 as well as variants of such polynucleotides which variants encode for ~~an~~a fragment, derivative or analog of the ~~polypeptide~~polynucleotide of SEQ ID NO:9 or the polypeptide encoded by SEQ ID NO:9. Such nucleotide variants include deletion variants, substitution variants and addition or insertion variants.

The paragraph beginning on page 24, line 25 has been amended to read:

The fragment, derivative or analog of the ~~polypeptide~~polynucleotide of SEQ ID NO:9 or ~~that~~the polypeptide encoded by the polynucleotide of SEQ ID NO:9 may be (i) one in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the

genetic code, or (ii) one in which one or more of the amino acid residues includes a substituent group, or (iii) one in which the mature polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol), or (iv) one in which the additional amino acids are fused to the mature polypeptide, such as a leader or secretory sequence or a sequence which is employed for purification of the mature polypeptide or a proprotein sequence. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art from the teachings herein.

In the claims:

Claim 2 has been cancelled.

Claim 1 has been amended to read:

1(amended). An isolated polypeptide comprising a truncated tryptophanyl-tRNA synthetase polypeptide comprising a Rossmann fold nucleotide binding domain, wherein the isolated polypeptide is capable of regulating vascular endothelial cell function and has a size of at least about 46 kilodaltons relative to full length tryptophanyl-tRNA synthetase having a size of about 54 kilodaltons.

Claim 3 has been amended to read:

3(amended). The isolated polypeptide of claim 1, wherein the truncated tryptophanyl-tRNA synthetase polypeptide has amino-terminal truncation.

Claim 4 has been amended to read:

4(amended). The isolated polypeptide of claim 1, wherein the polypeptide is ~~angiogenic~~angiostatic.

Claim 6 has been amended to read:

6(twice amended). The isolated polypeptide of claim 1, wherein the truncated tryptophanyl-tRNA synthetase polypeptide is a member of the group consisting of

a polypeptide consisting essentially of amino acid residues 48-471 of SEQ ID NO:10;

a polypeptide consisting essentially of amino acid residues 71-471 of SEQ ID NO:10;

a polypeptide of approximately 47 kD molecular weight produced by cleavage of the polypeptide of SEQ ID NO:10 with polymorphonuclear leucocyte elastase; and

fragments thereof comprising the amino acid sequence -Asp-Leu-Thr-.